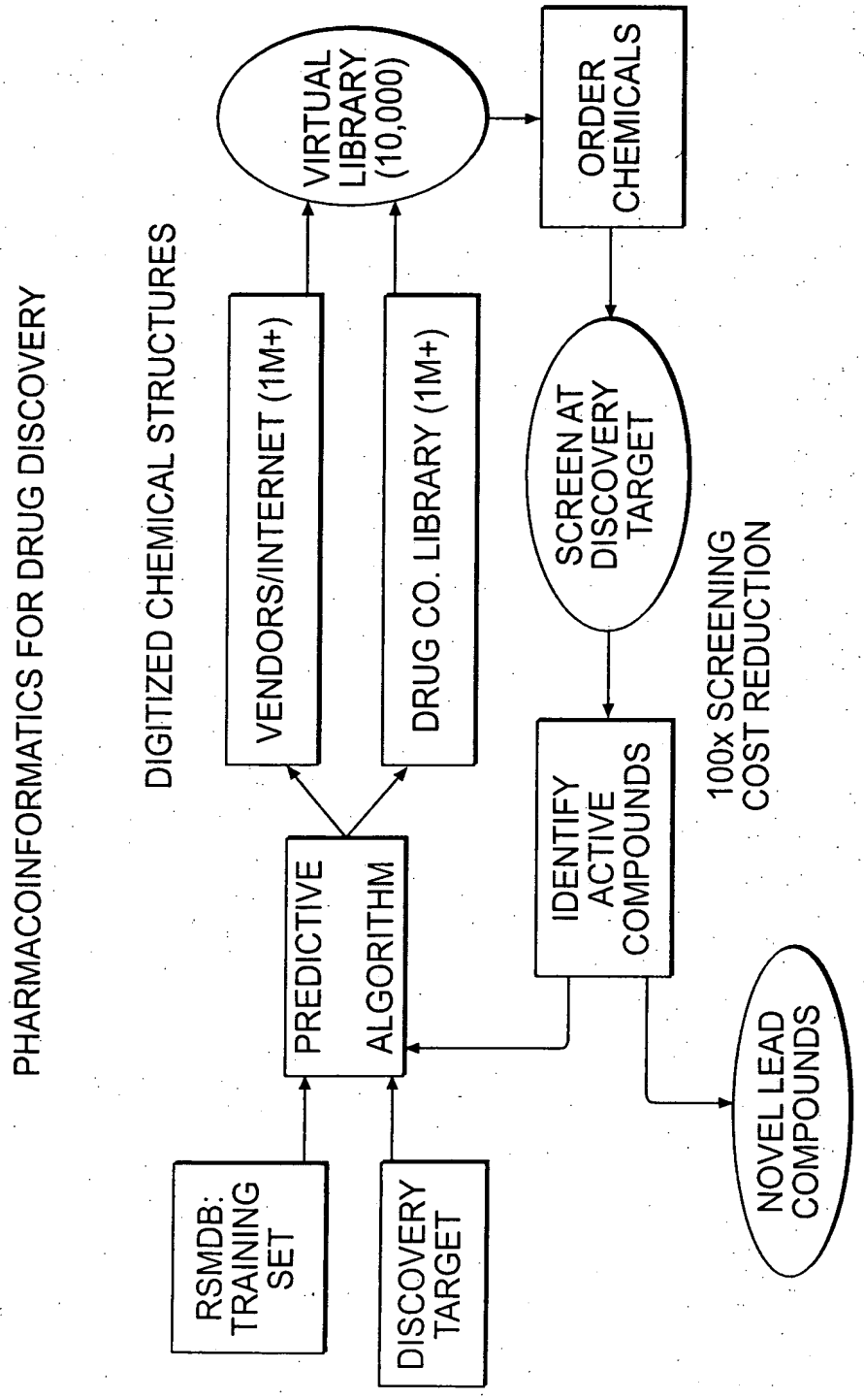


FIG. 1

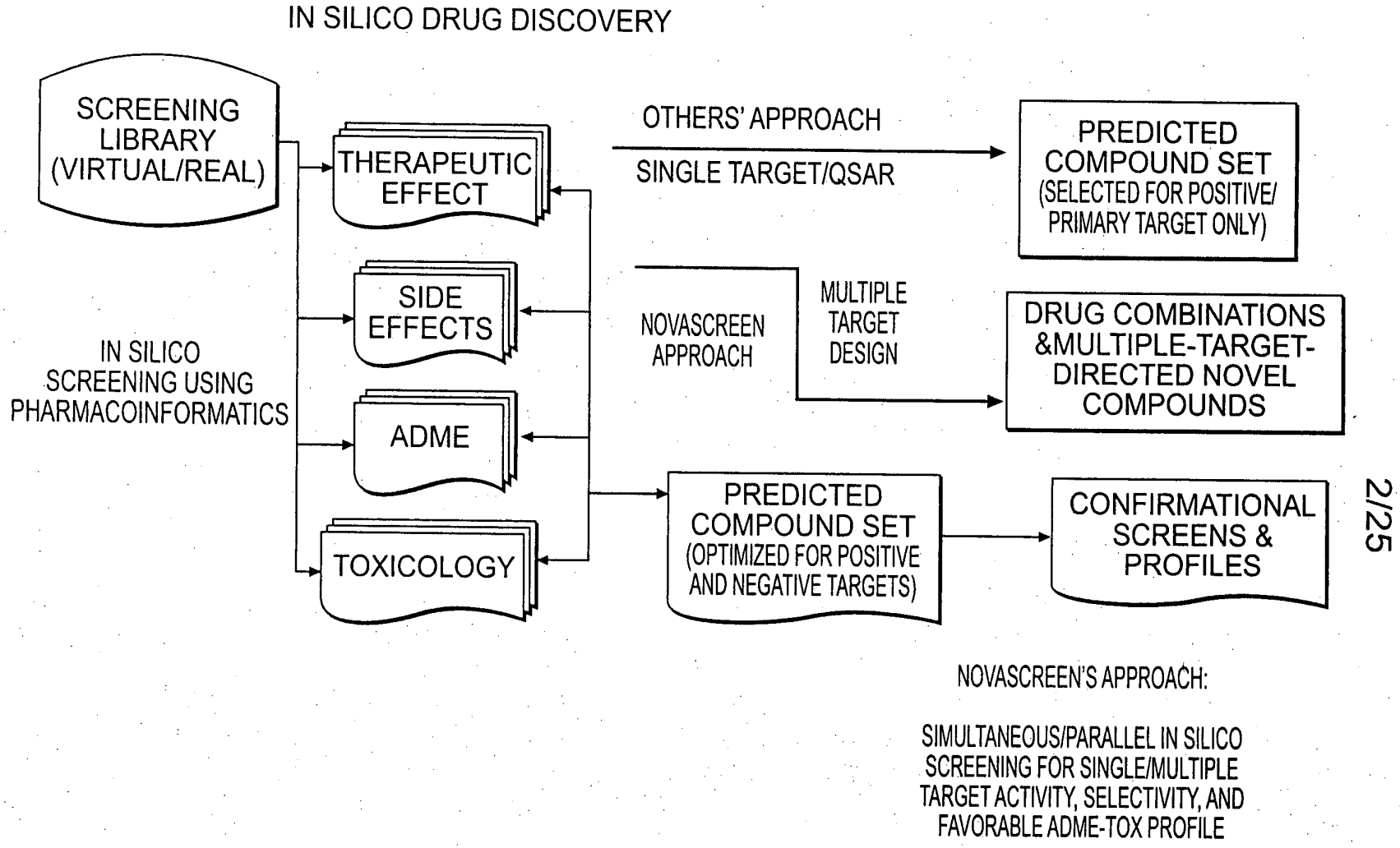

IN SILICO DRUG DISCOVERY
SCREENING LIBRARY (VIRTUAL/REAL)
IN SILICO SCREENING USING PHARMACOINFORMATICS
THERAPEUTIC EFFECT
SIDE EFFECTS
ADME
TOXICOLOGY
OTHERS' APPROACH
SINGLE TARGET/QSAR
PREDICTED COMPOUND SET (SELECTED FOR POSITIVE/ PRIMARY TARGET ONLY)
NOVASCREEN APPROACH
MULTIPLE TARGET DESIGN
DRUG COMBINATIONS &MULTIPLE-TARGET-DIRECTED NOVEL COMPOUNDS
PREDICTED COMPOUND SET (OPTIMIZED FOR POSITIVE AND NEGATIVE TARGETS)
CONFIRMATIONAL SCREENS & PROFILES
NOVASCREEN'S APPROACH:
SIMULTANEOUS/PARALLEL IN SILICO SCREENING FOR SINGLE/MULTIPLE TARGET ACTIVITY, SELECTIVITY, AND FAVORABLE ADME-TOX PROFILE

FIG. 2

$$\Sigma P_T = \Sigma P_D - \Sigma P_{UD}$$

$$\Sigma P_D = \Sigma P_{prot\_1} + \Sigma P_{prot\_2} + \Sigma P_{prot\_n} + \cdots + \Sigma P_{phys\_1} + \Sigma P_{phys\_2} + \Sigma P_{phys\_n} \cdots$$

$$\Sigma P_{UD} = \Sigma P_{prot\_1u} + \Sigma P_{prot\_2u} + \Sigma P_{prot\_nu} \cdots + \Sigma P_{phys\_1u} + \Sigma P_{phys\_2u} + \Sigma P_{phys\_nu} \cdots$$

FIG. 3

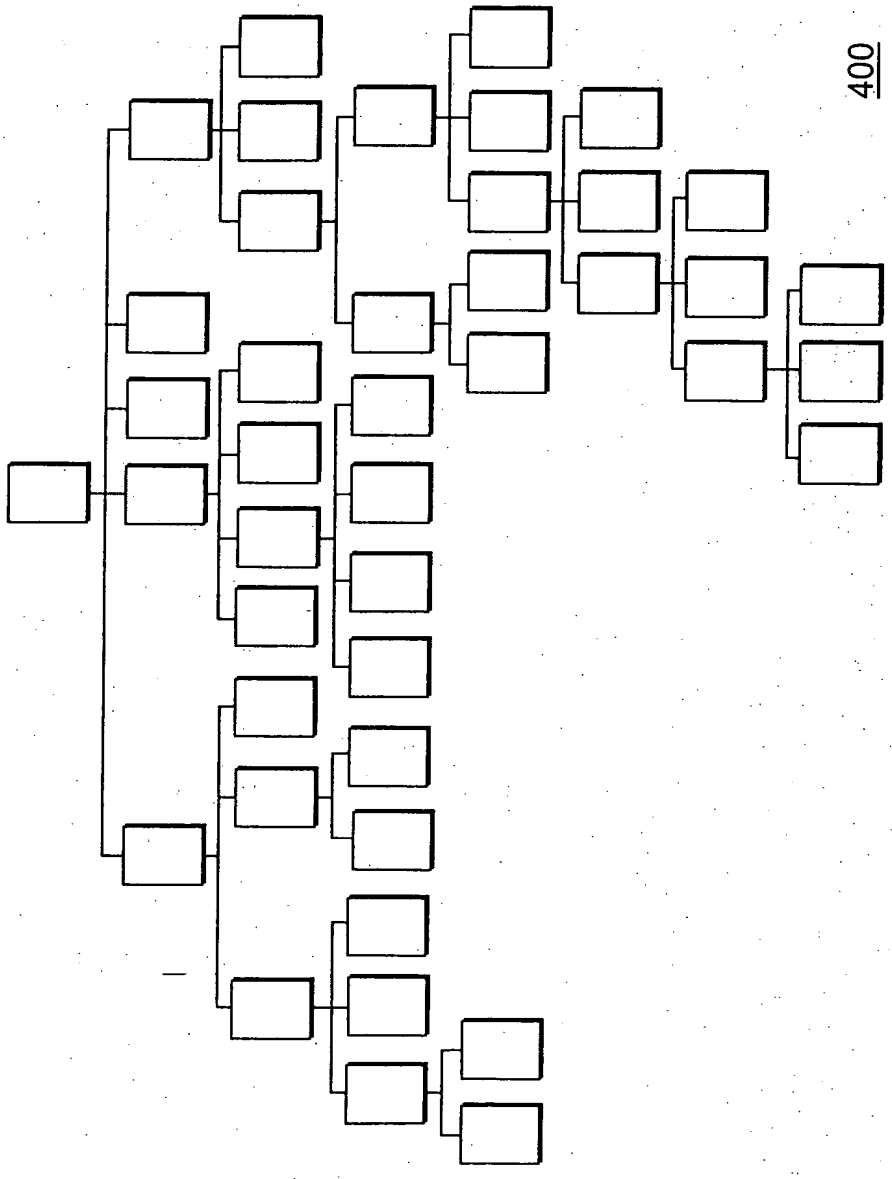
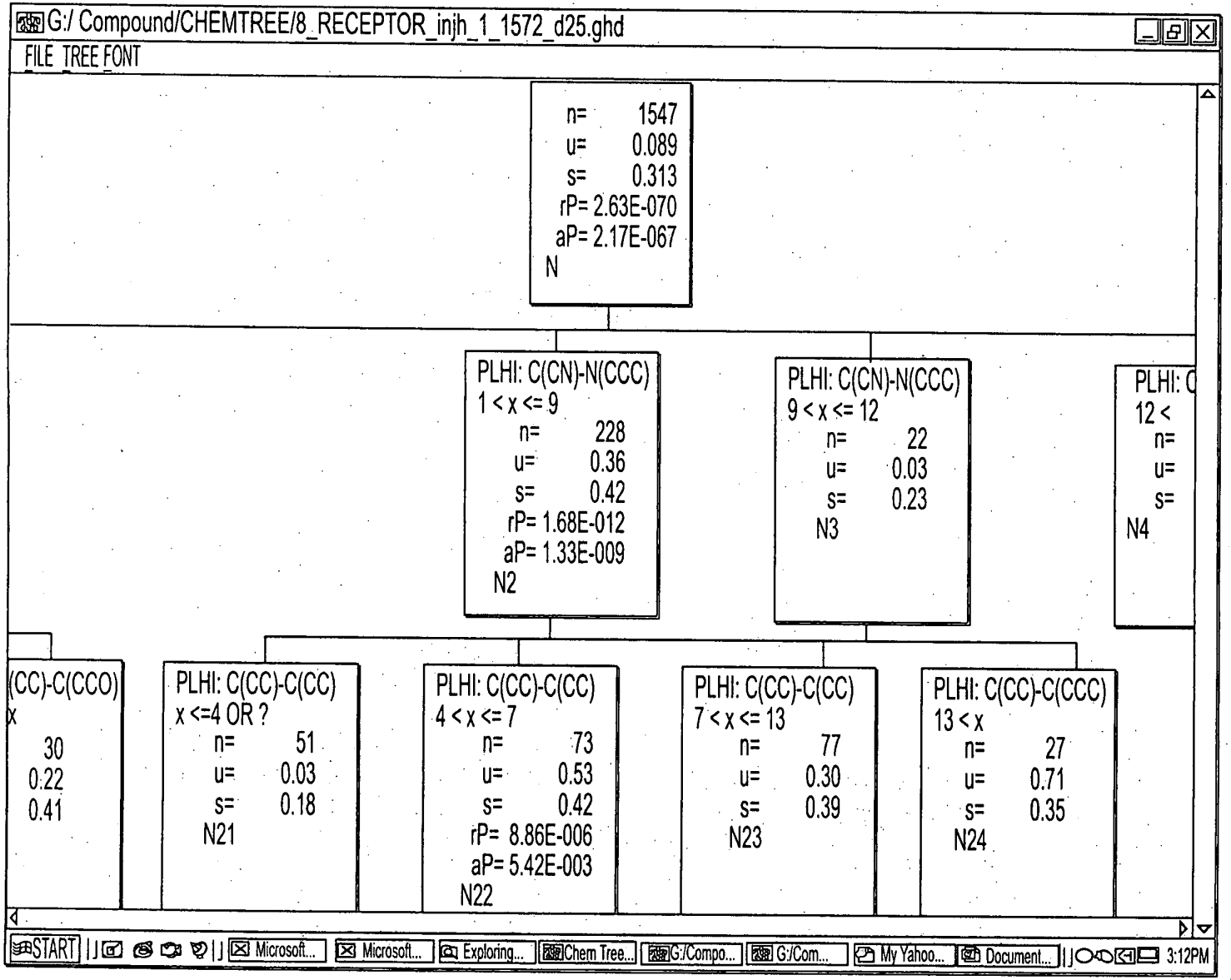


FIG. 4


G:/ Compound/CHEMTREE/8_RECEPTOR_injh_1_1572_d25.ghd
FILE TREE FONT
n= 1547
u= 0.089
s= 0.313
rP= 2.63E-070
aP= 2.17E-067
N
PLHI: C(CN)-N(CCC)
1 < x <= 9
n= 228
u= 0.36
s= 0.42
rP= 1.68E-012
aP= 1.33E-009
N2
PLHI: C(CN)-N(CCC)
9 < x <= 12
n= 22
u= 0.03
s= 0.23
N3
PLHI: C
12 <
n=
u=
s=
N4
(CC)-C(CCO)
x
30
0.22
0.41
PLHI: C(CC)-C(CC)
x <=4 OR ?
n= 51
u= 0.03
s= 0.18
N21
PLHI: C(CC)-C(CC)
4 < x <= 7
n= 73
u= 0.53
s= 0.42
rP= 8.86E-006
aP= 5.42E-003
N22
PLHI: C(CC)-C(CC)
7 < x <= 13
n= 77
u= 0.30
s= 0.39
N23
PLHI: C(CC)-C(CCC)
13 < x
n= 27
u= 0.71
s= 0.35
N24
START
Microsoft...
Microsoft...
Exploring...
Chem Tree...
G:/Compo...
G:/Com...
My Yahoo...
Document...
3:12PM

500

FIG. 5

- PLHI: N(CC) - N(CC) X = 3
  - PLLO: C(CCC) - N(CC) X = 2
  - PLHI: C(CCC) - N(CC) X = 5
  - PLLO: C(CNN) - N(CC) X = 1
  - PLHI: C(CNN) - N(CC) X = 2

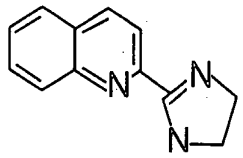


FIG. 6

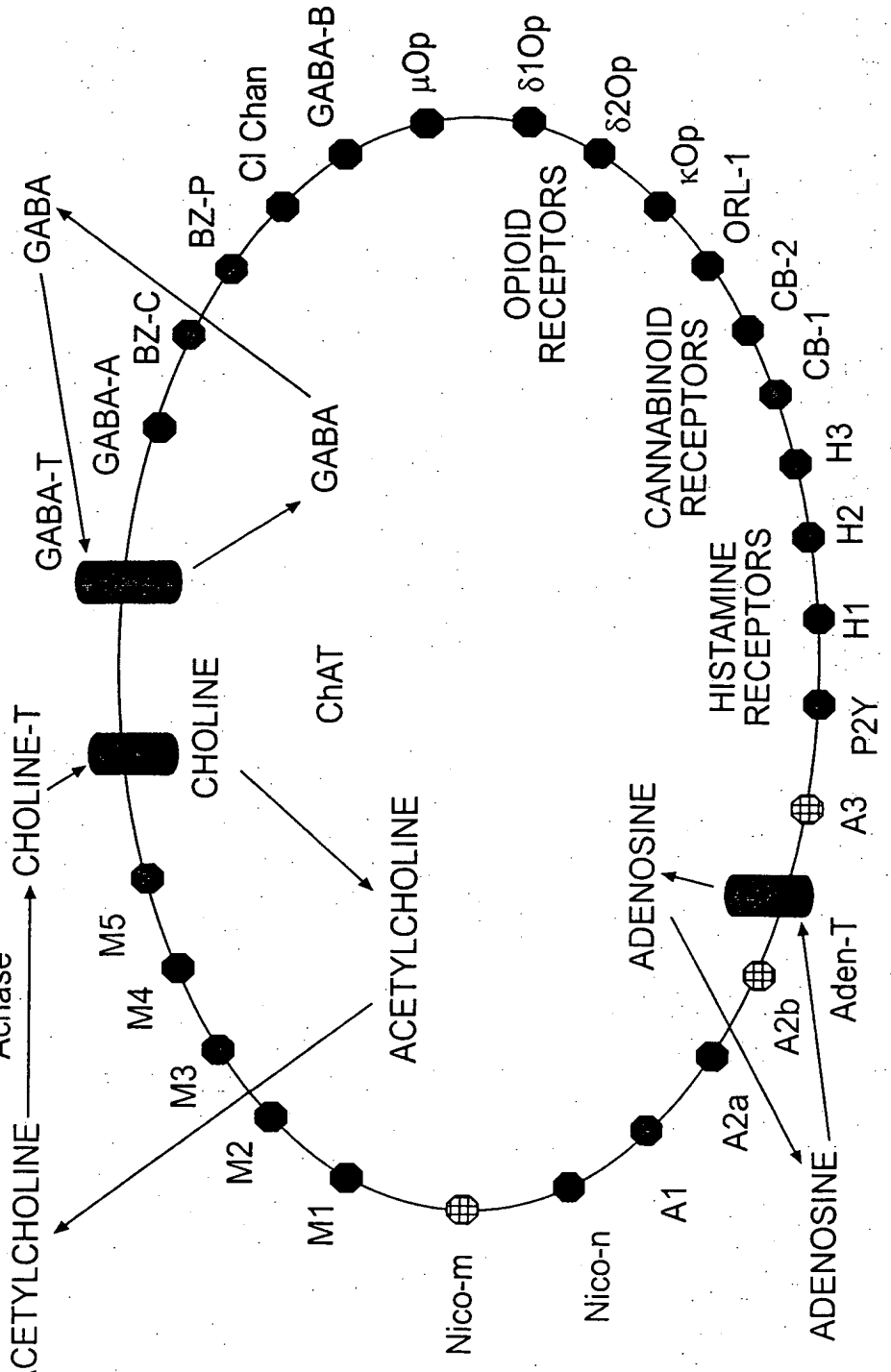

ACETYLCHOLINE
Achase
CHOLINE-T
CHOLINE
ACETYLCHOLINE
ChAT
M5
M4
M3
M2
M1
Nico-m
Nico-n
A1
A2a
A2b
A3
ADENOSINE
Aden-T
ADENOSINE
P2Y
H1
H2
H3
HISTAMINE RECEPTORS
CB-1
CB-2
CANNABINOID RECEPTORS
ORL-1
κOp
δ2Op
δ1Op
μOp
OPIOID RECEPTORS
GABA-B
Cl Chan
BZ-P
BZ-C
GABA-A
GABA-T
GABA
GABA

FIG. 7

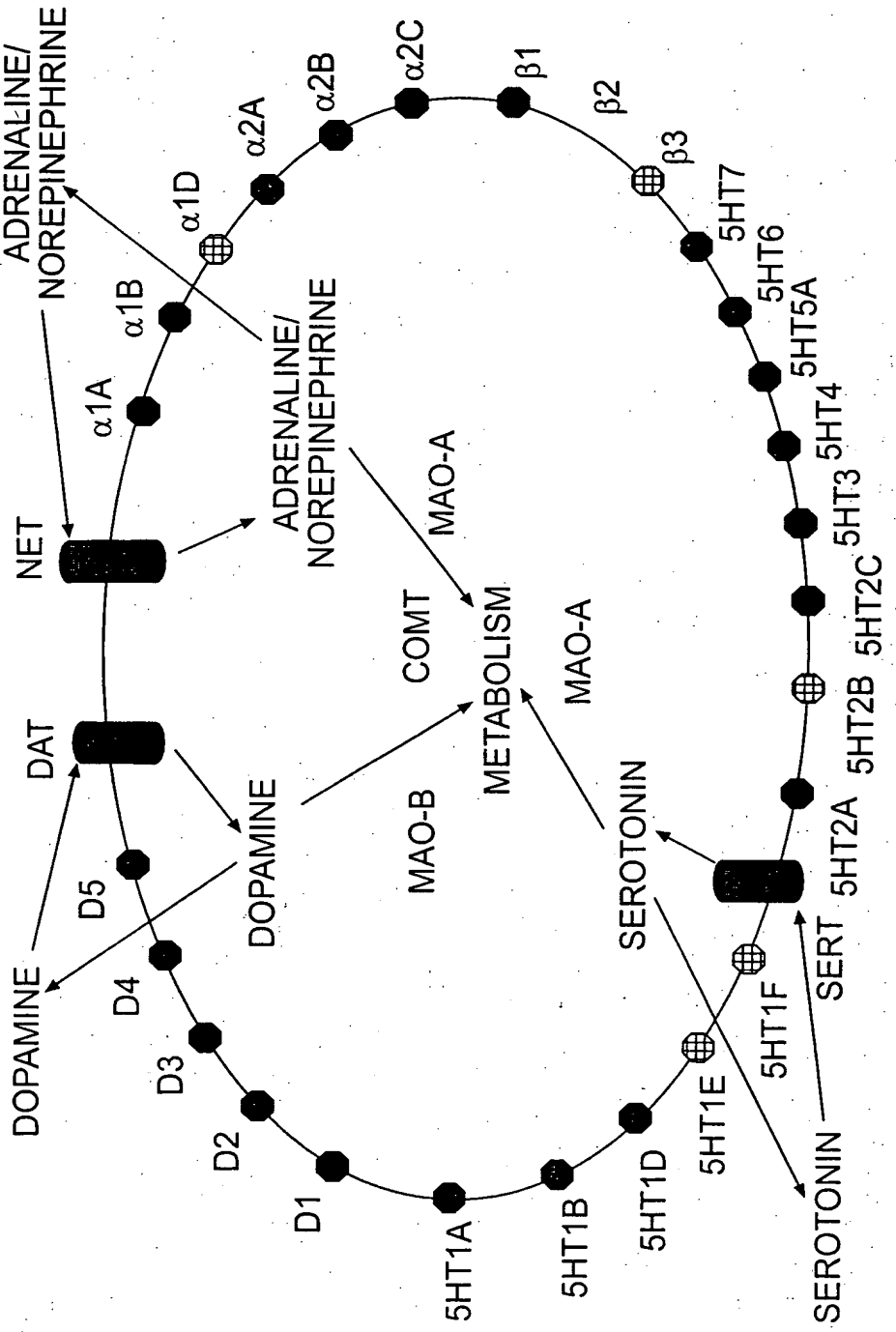

ADRENALINE/
NOREPINEPHRINE
α1A
α1B
α1D
α2A
α2B
α2C
β1
β2
β3
5HT7
5HT6
5HT5A
5HT4
5HT3
5HT2C
5HT2B
5HT2A
NET
ADRENALINE/
NOREPINEPHRINE
MAO-A
COMT
METABOLISM
MAO-A
DAT
DOPAMINE
MAO-B
SEROTONIN
D5
D4
D3
D2
D1
5HT1A
5HT1B
5HT1D
5HT1E
5HT1F
SERT
DOPAMINE
SEROTONIN

FIG. 8

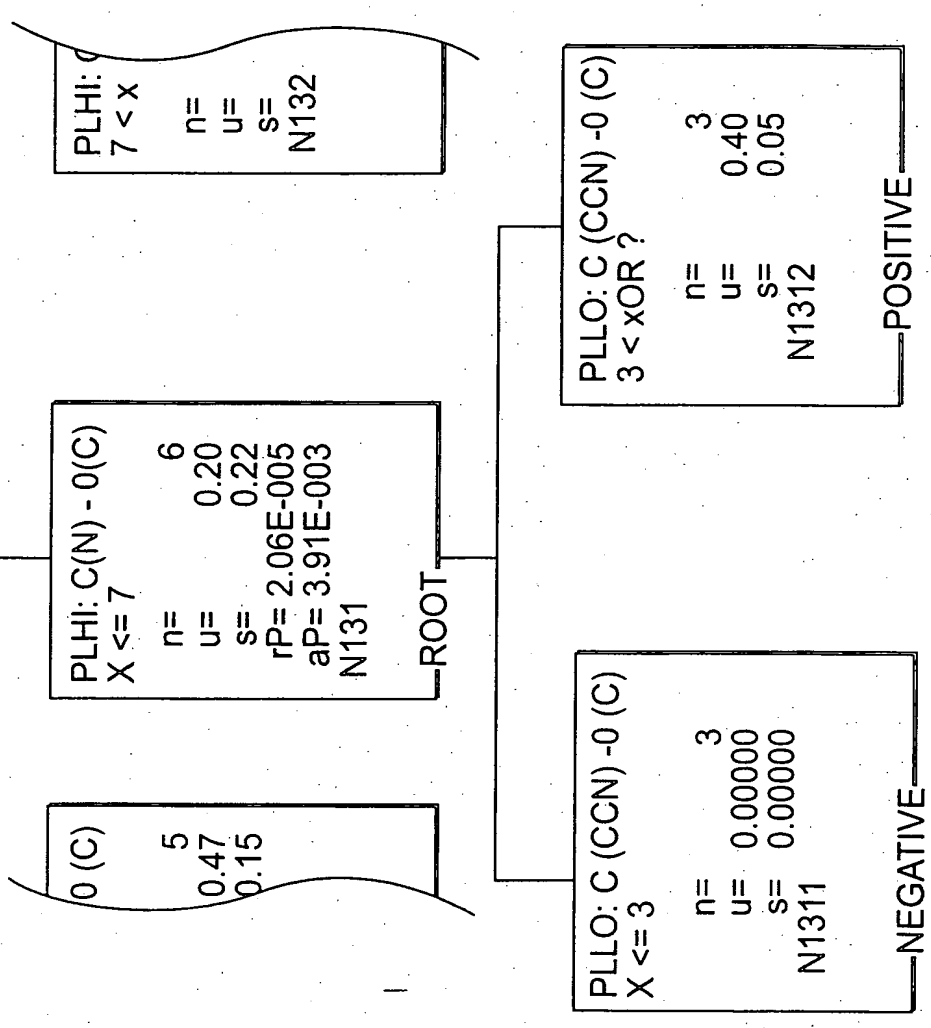

0 (C)
5
0.47
0.15
PLHI: C(N) - 0(C)
X <= 7
n= 6
u= 0.20
s= 0.22
rP= 2.06E-005
aP= 3.91E-003
N131
ROOT
PLHI:
7 < x
n=
u=
s=
N132
PLLO: C (CCN) -0 (C)
X <= 3
n= 3
u= 0.00000
s= 0.00000
N1311
NEGATIVE
PLLO: C (CCN) -0 (C)
3 < xOR ?
n= 3
u= 0.40
s= 0.05
N1312
POSITIVE

FIG. 9

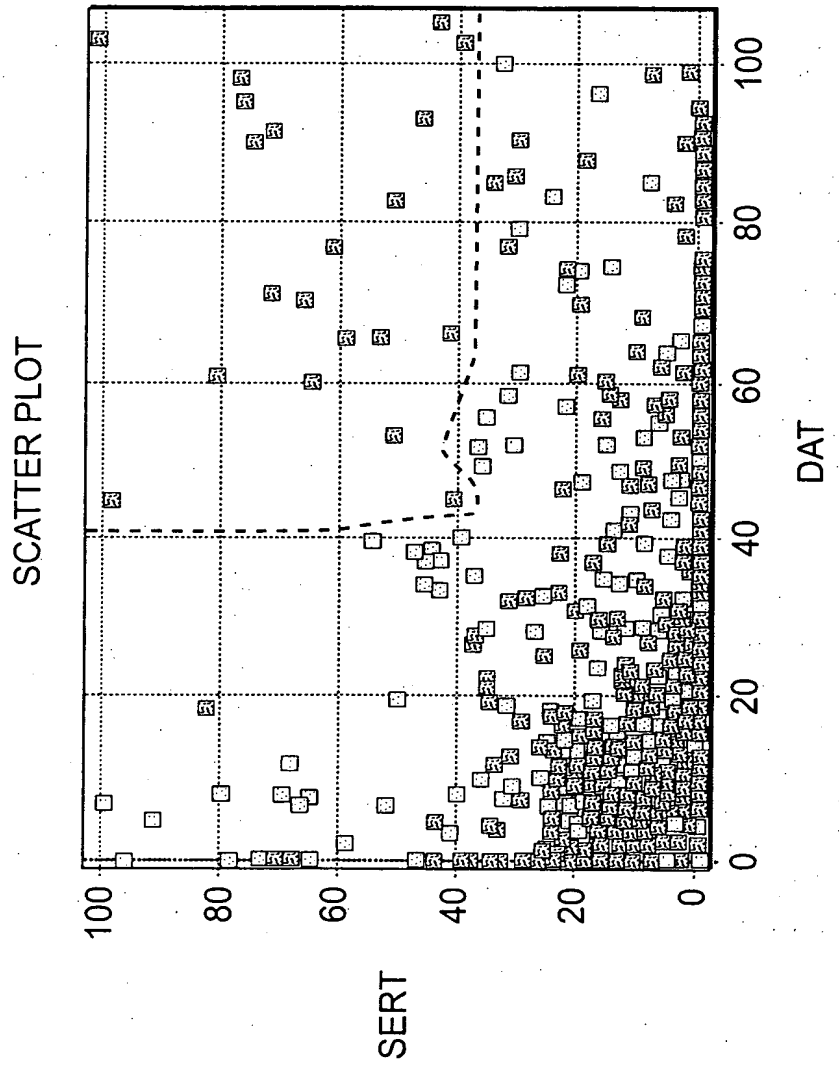


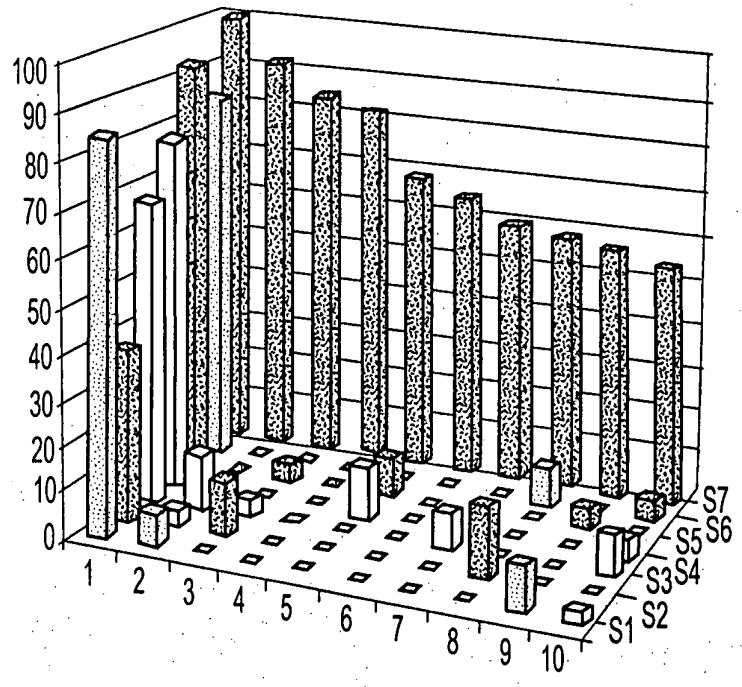
FIG. 10

PHARMACOINFORMATICS
SINGLE STEP APPROACH TO OPTIMIZED LEADS

AN EXAMPLE OF FINDING BETTER AND CLEANER DRUG CANDIDATES

IN SILICO SCREEN 240,000 CMPDS

- 400 COMPOUNDS
- 34 HITS
- 5 STRUCTURAL CLASSES
- 9 HITS WITH DESIRED TARGET SPECIFICITY



CONFIDENTIAL

11/25

FIG. 11

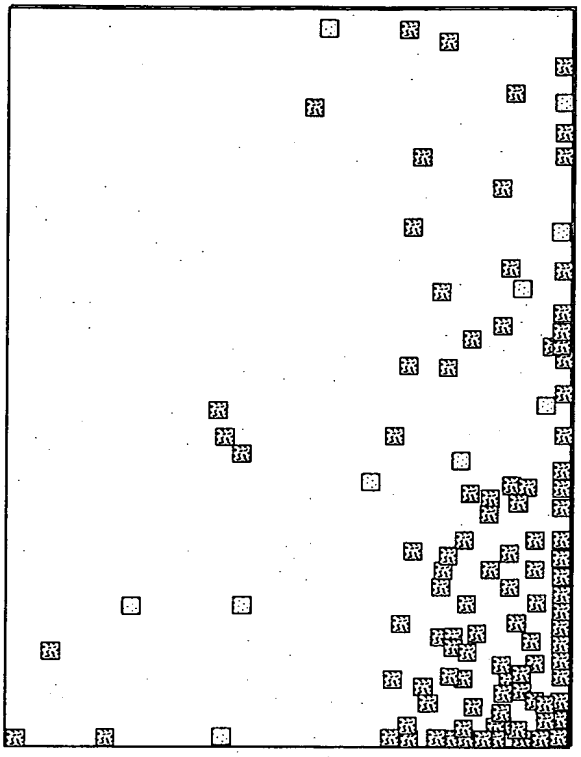


FIG. 12b

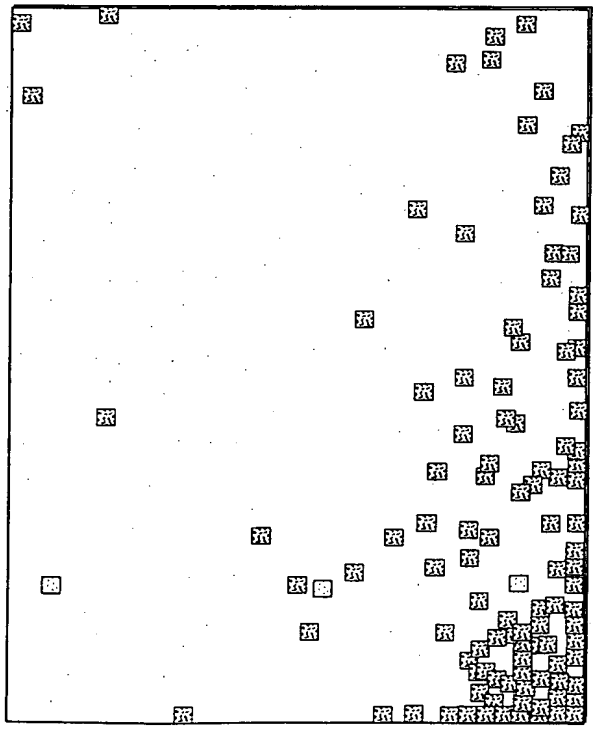


FIG. 12a

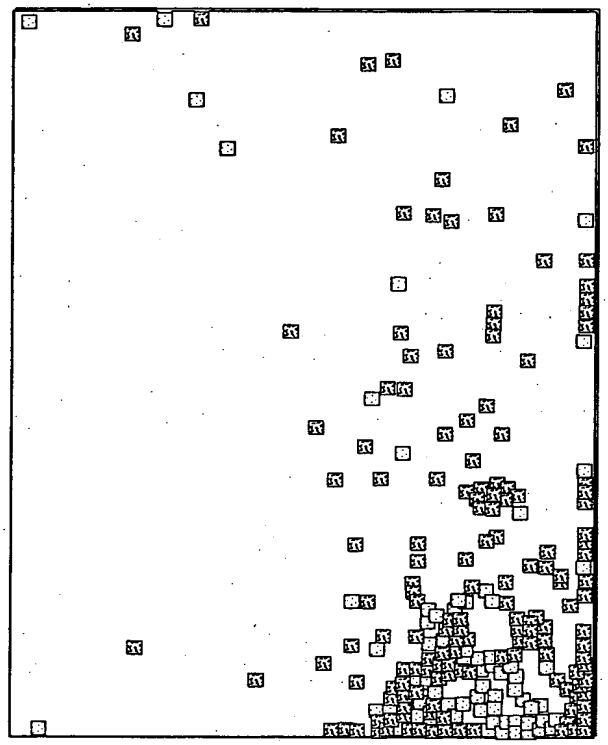


FIG. 12d

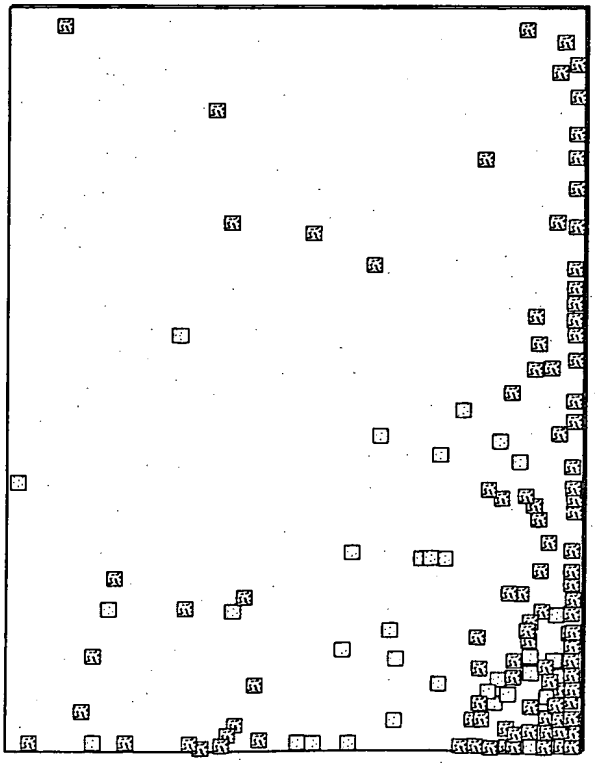


FIG. 12c

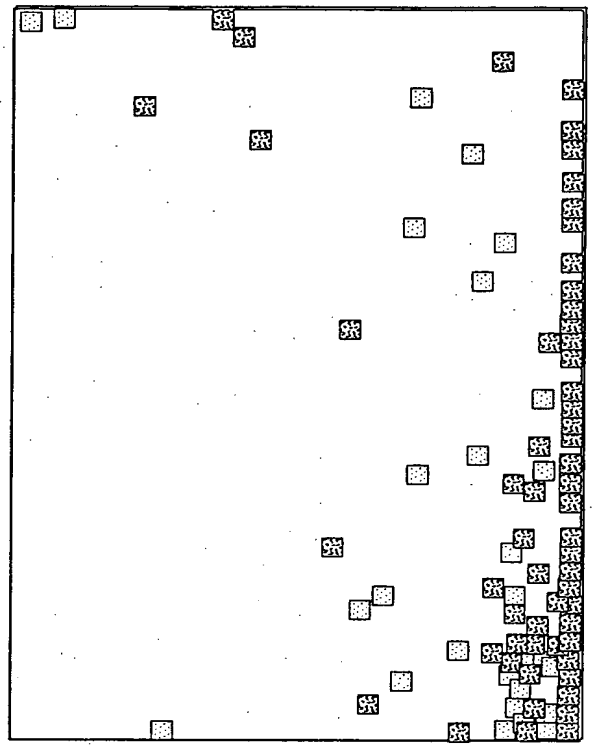


FIG. 12f

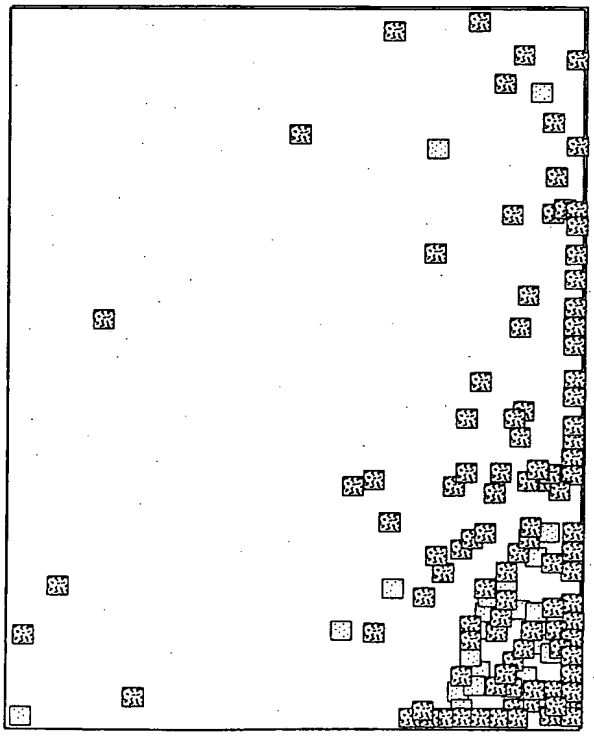


FIG. 12e

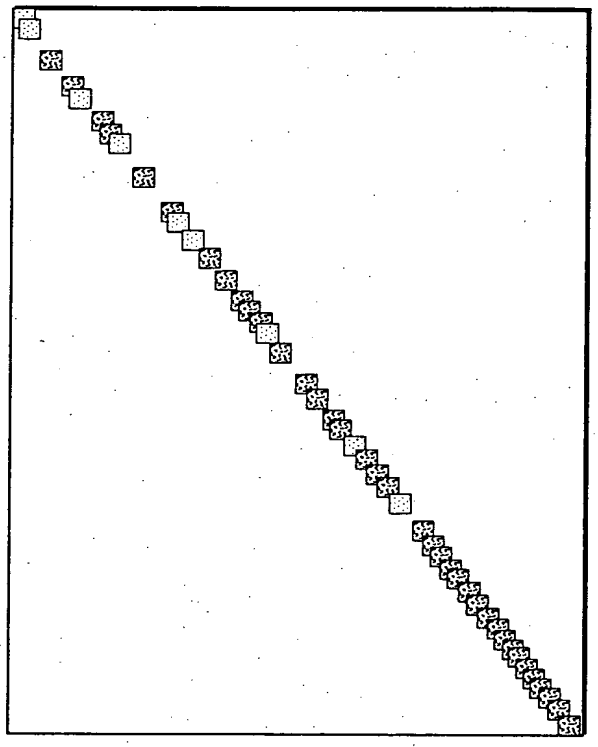


FIG. 12g

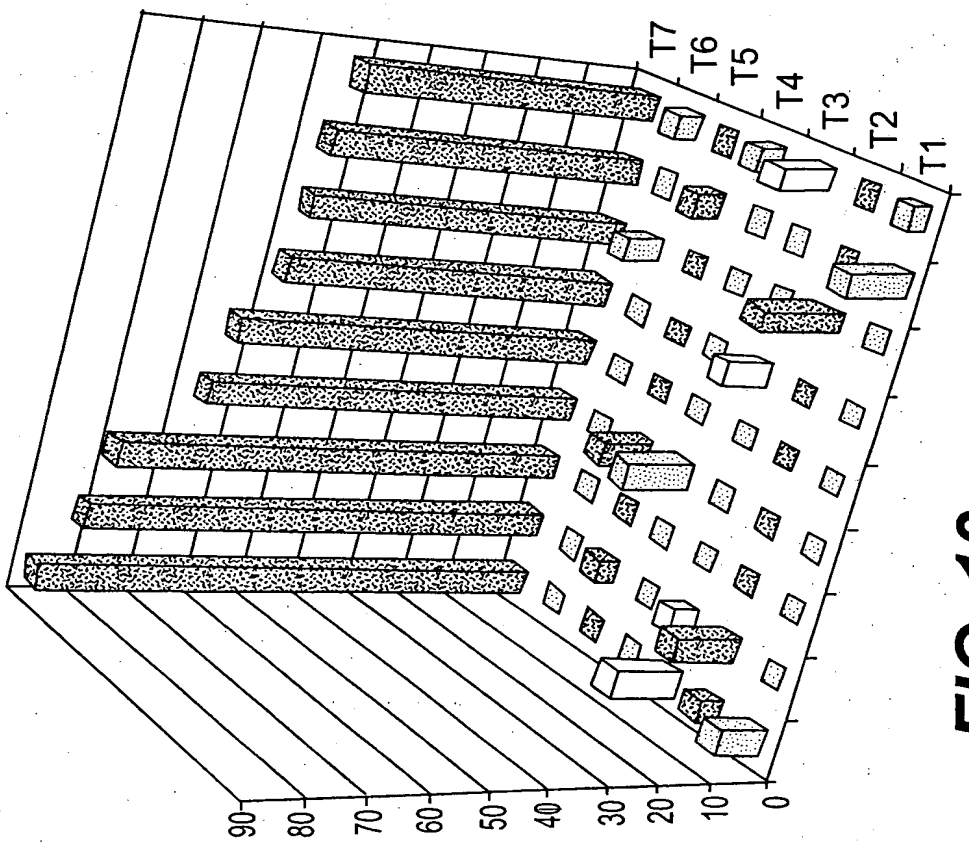


FIG. 13

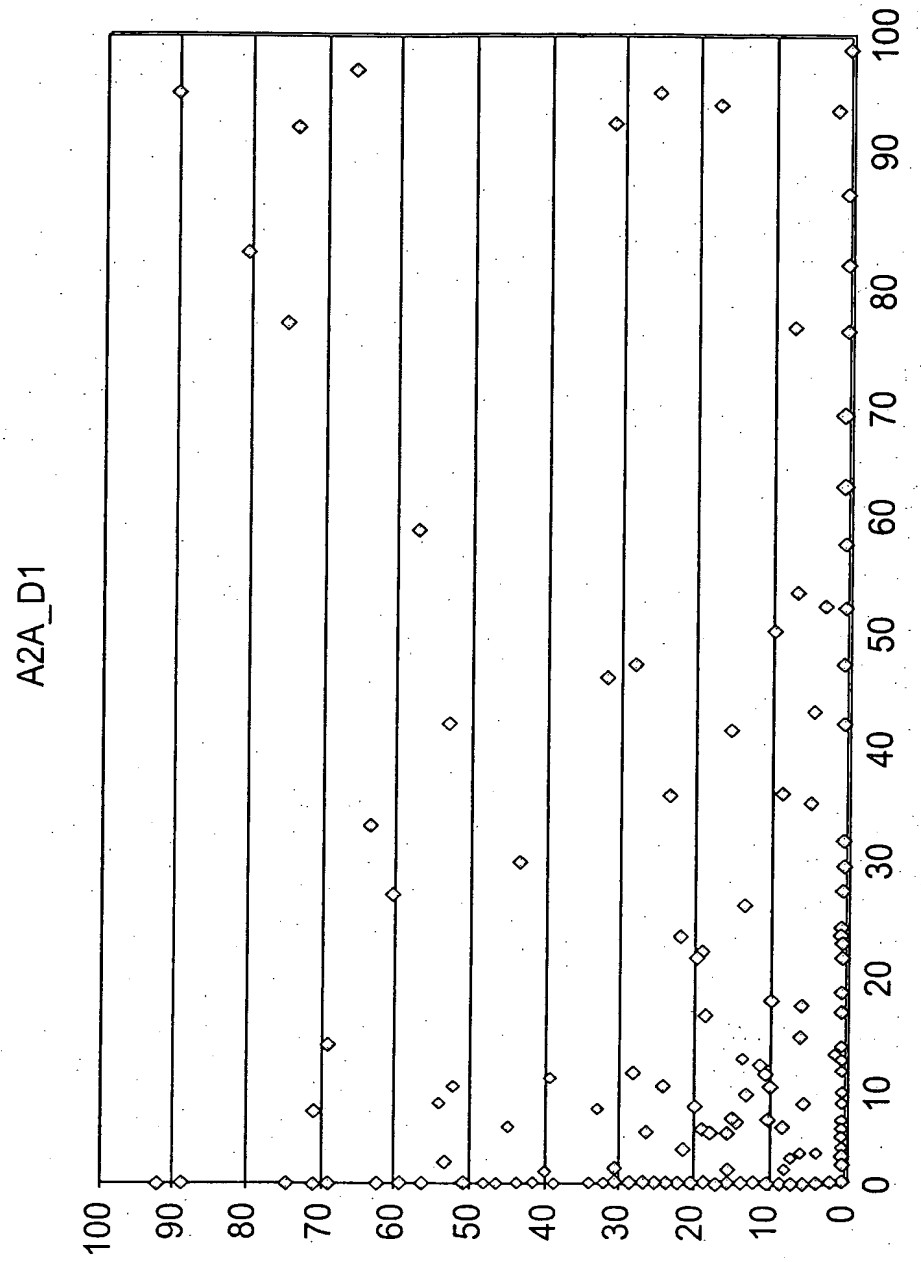


FIG. 14

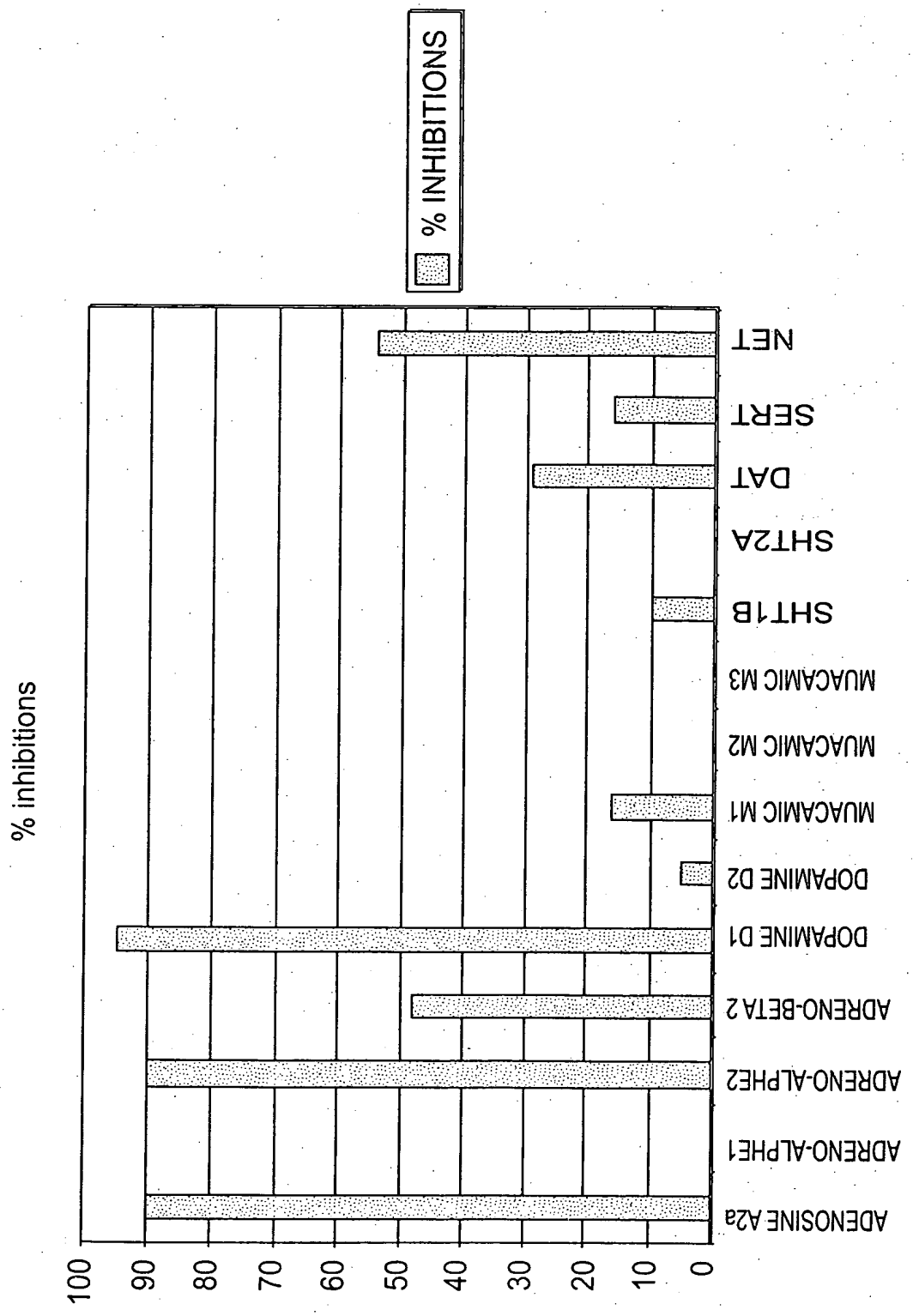

% INHIBITIONS
% inhibitions
100
90
80
70
60
50
40
30
20
10
0
ADENOSINE A2a
ADRENO-ALPHE1
ADRENO-ALPHE2
ADRENO-BETA 2
DOPAMINE D1
DOPAMINE D2
MUACAMIC M1
MUACAMIC M2
MUACAMIC M3
SHT1B
SHT2A
DAT
SERT
NET

FIG. 15

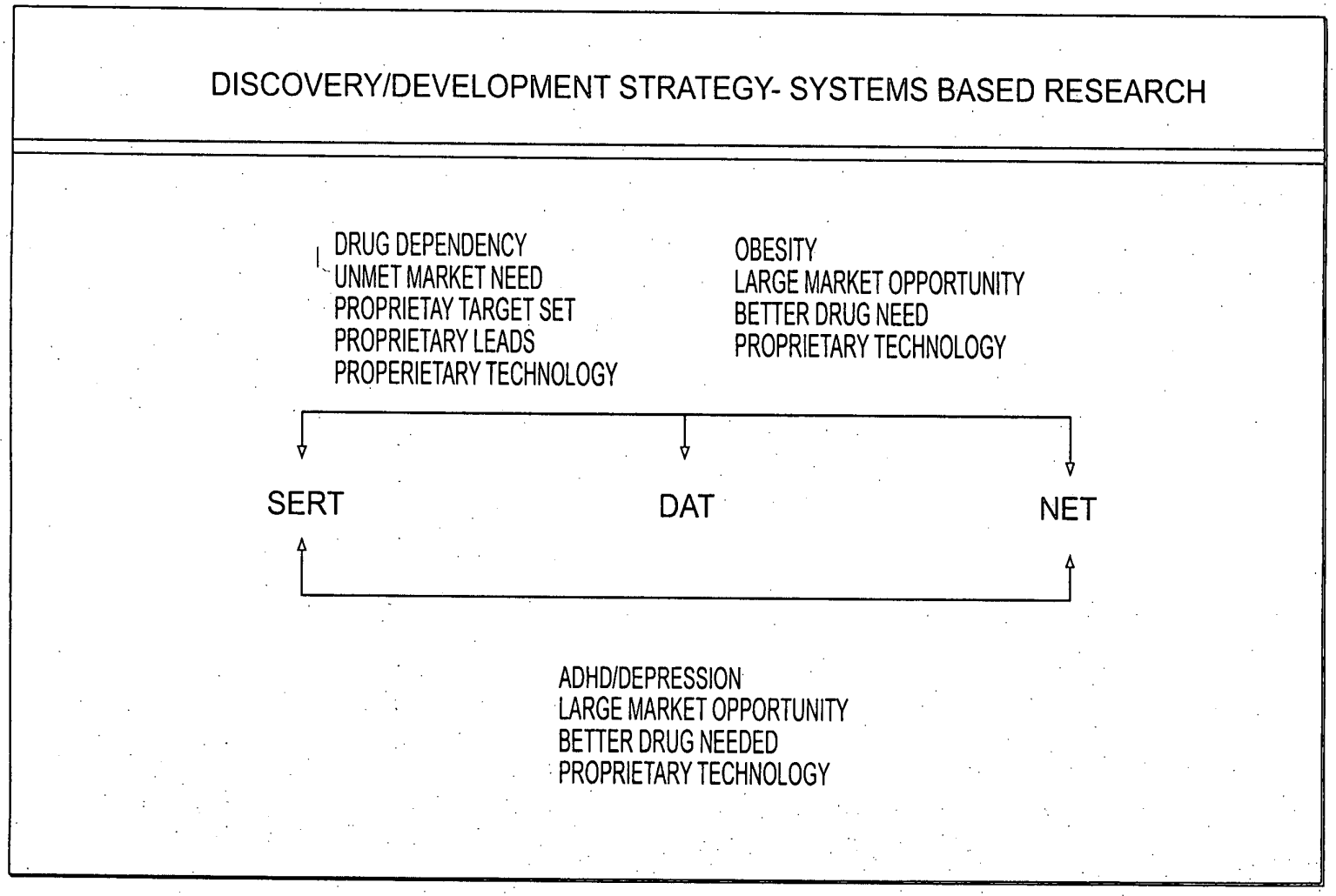

DISCOVERY/DEVELOPMENT STRATEGY- SYSTEMS BASED RESEARCH
DRUG DEPENDENCY
UNMET MARKET NEED
PROPRIETAY TARGET SET
PROPRIETARY LEADS
PROPERIETARY TECHNOLOGY
OBESITY
LARGE MARKET OPPORTUNITY
BETTER DRUG NEED
PROPRIETARY TECHNOLOGY
SERT
DAT
NET
ADHD/DEPRESSION
LARGE MARKET OPPORTUNITY
BETTER DRUG NEEDED
PROPRIETARY TECHNOLOGY

FIG. 16

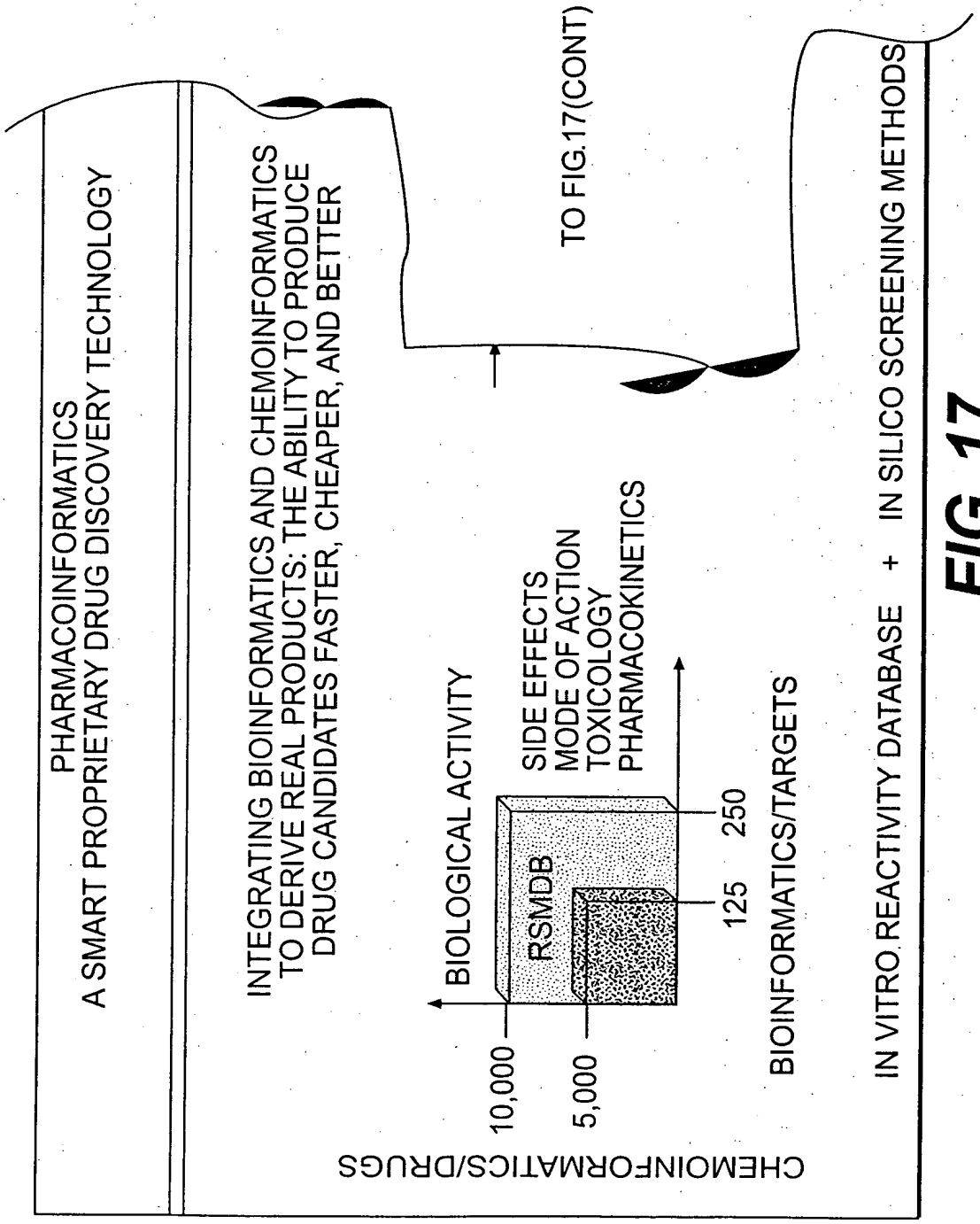

PHARMACOINFORMATICS
A SMART PROPRIETARY DRUG DISCOVERY TECHNOLOGY
INTEGRATING BIOINFORMATICS AND CHEMOINFORMATICS
TO DERIVE REAL PRODUCTS: THE ABILITY TO PRODUCE
DRUG CANDIDATES FASTER, CHEAPER, AND BETTER
TO FIG.17(CONT)
CHEMOINFORMATICS/DRUGS
BIOLOGICAL ACTIVITY
10,000
RSMDB
5,000
SIDE EFFECTS
MODE OF ACTION
TOXICOLOGY
PHARMACOKINETICS
125
250
BIOINFORMATICS/TARGETS
IN VITRO REACTIVITY DATABASE + IN SILICO SCREENING METHODS

FIG. 17

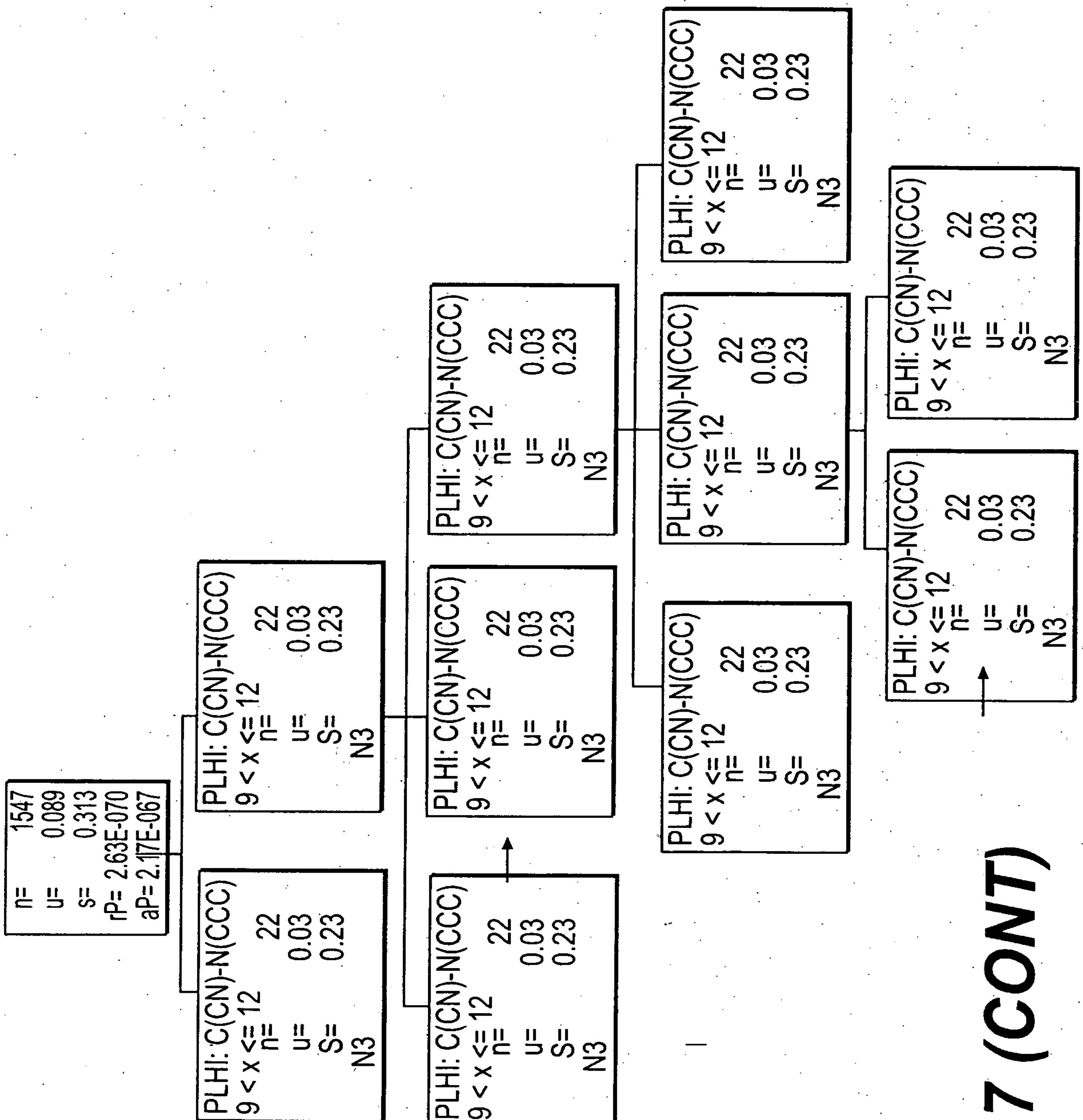

n= 1547
u= 0.089
s= 0.313
rP= 2.63E-070
aP= 2.17E-067
PLHI: C(CN)-N(CCC)
9 < x <= 12
n= 22
u= 0.03
S= 0.23
N3

FIG. 17 (CONT)

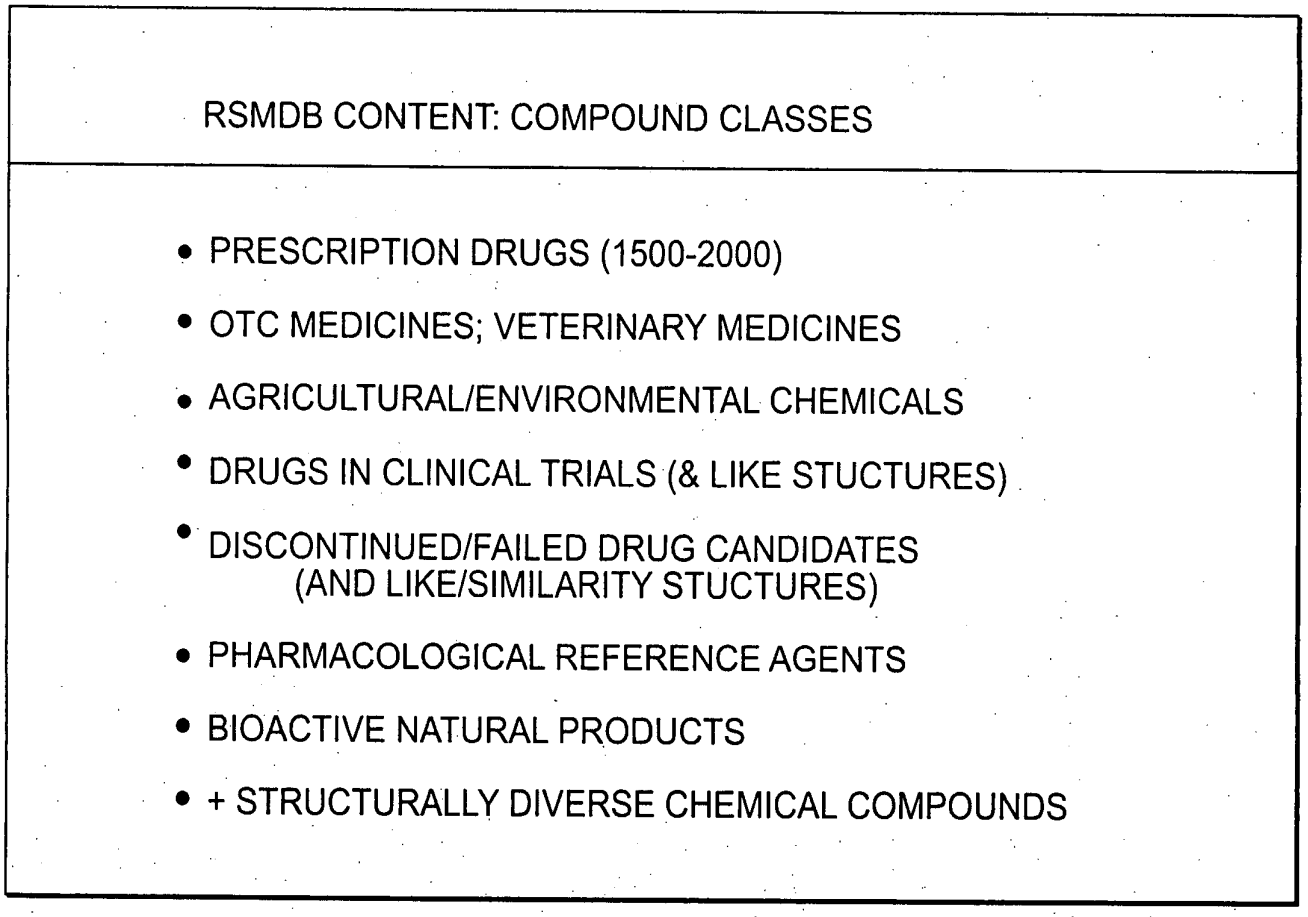

RSMDB CONTENT: COMPOUND CLASSES
• PRESCRIPTION DRUGS (1500-2000)
• OTC MEDICINES; VETERINARY MEDICINES
• AGRICULTURAL/ENVIRONMENTAL CHEMICALS
• DRUGS IN CLINICAL TRIALS (& LIKE STUCTURES)
• DISCONTINUED/FAILED DRUG CANDIDATES (AND LIKE/SIMILARITY STUCTURES)
• PHARMACOLOGICAL REFERENCE AGENTS
• BIOACTIVE NATURAL PRODUCTS
• + STRUCTURALLY DIVERSE CHEMICAL COMPOUNDS

FIG. 18

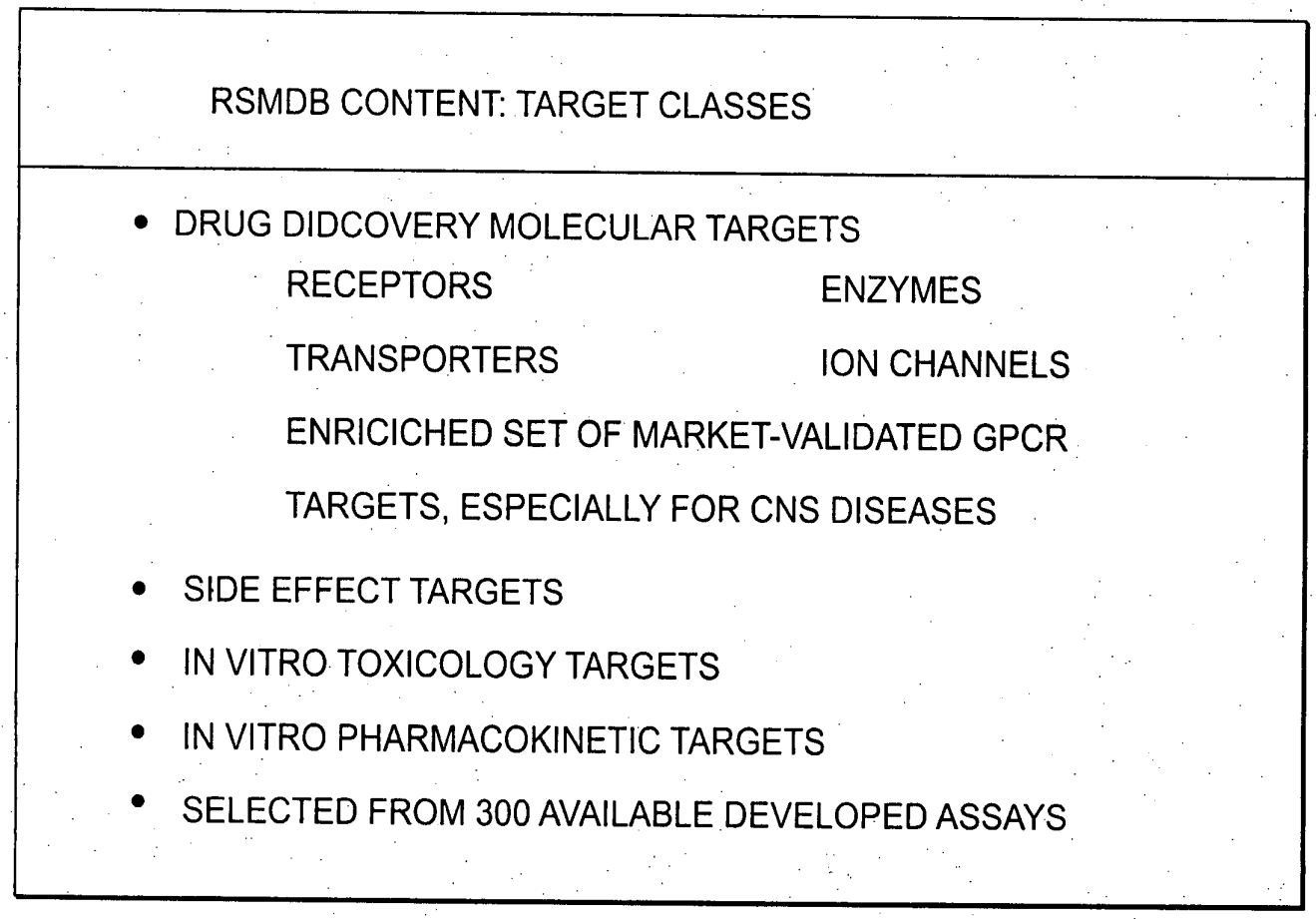

RSMDB CONTENT: TARGET CLASSES
• DRUG DIDCOVERY MOLECULAR TARGETS
RECEPTORS
ENZYMES
TRANSPORTERS
ION CHANNELS
ENRICICHED SET OF MARKET-VALIDATED GPCR
TARGETS, ESPECIALLY FOR CNS DISEASES
• SIDE EFFECT TARGETS
• IN VITRO TOXICOLOGY TARGETS
• IN VITRO PHARMACOKINETIC TARGETS
• SELECTED FROM 300 AVAILABLE DEVELOPED ASSAYS

FIG. 19

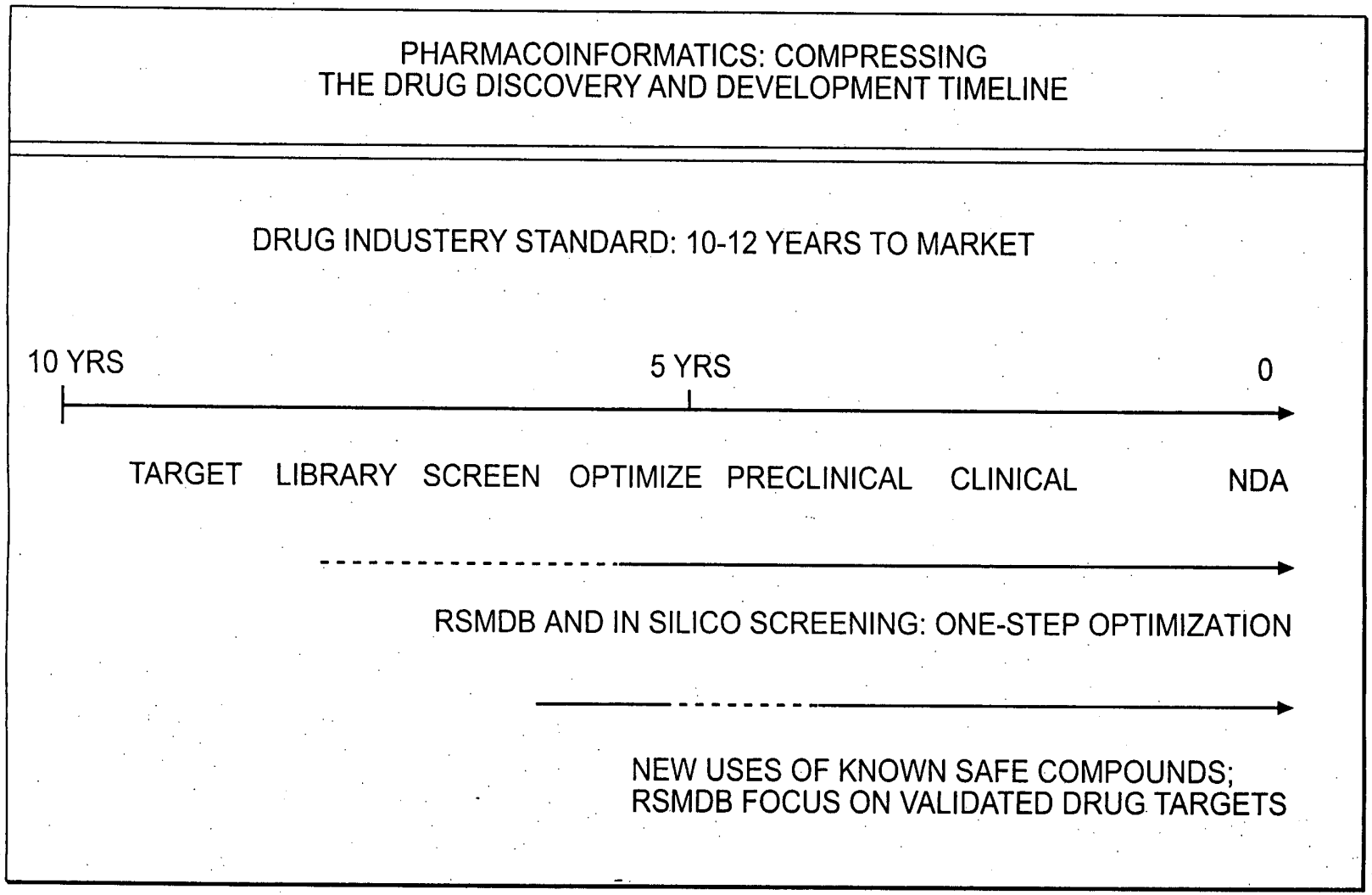

PHARMACOINFORMATICS: COMPRESSING
THE DRUG DISCOVERY AND DEVELOPMENT TIMELINE
DRUG INDUSTERY STANDARD: 10-12 YEARS TO MARKET
10 YRS
5 YRS
0
TARGET
LIBRARY
SCREEN
OPTIMIZE
PRECLINICAL
CLINICAL
NDA
RSMDB AND IN SILICO SCREENING: ONE-STEP OPTIMIZATION
NEW USES OF KNOWN SAFE COMPOUNDS;
RSMDB FOCUS ON VALIDATED DRUG TARGETS

FIG. 20

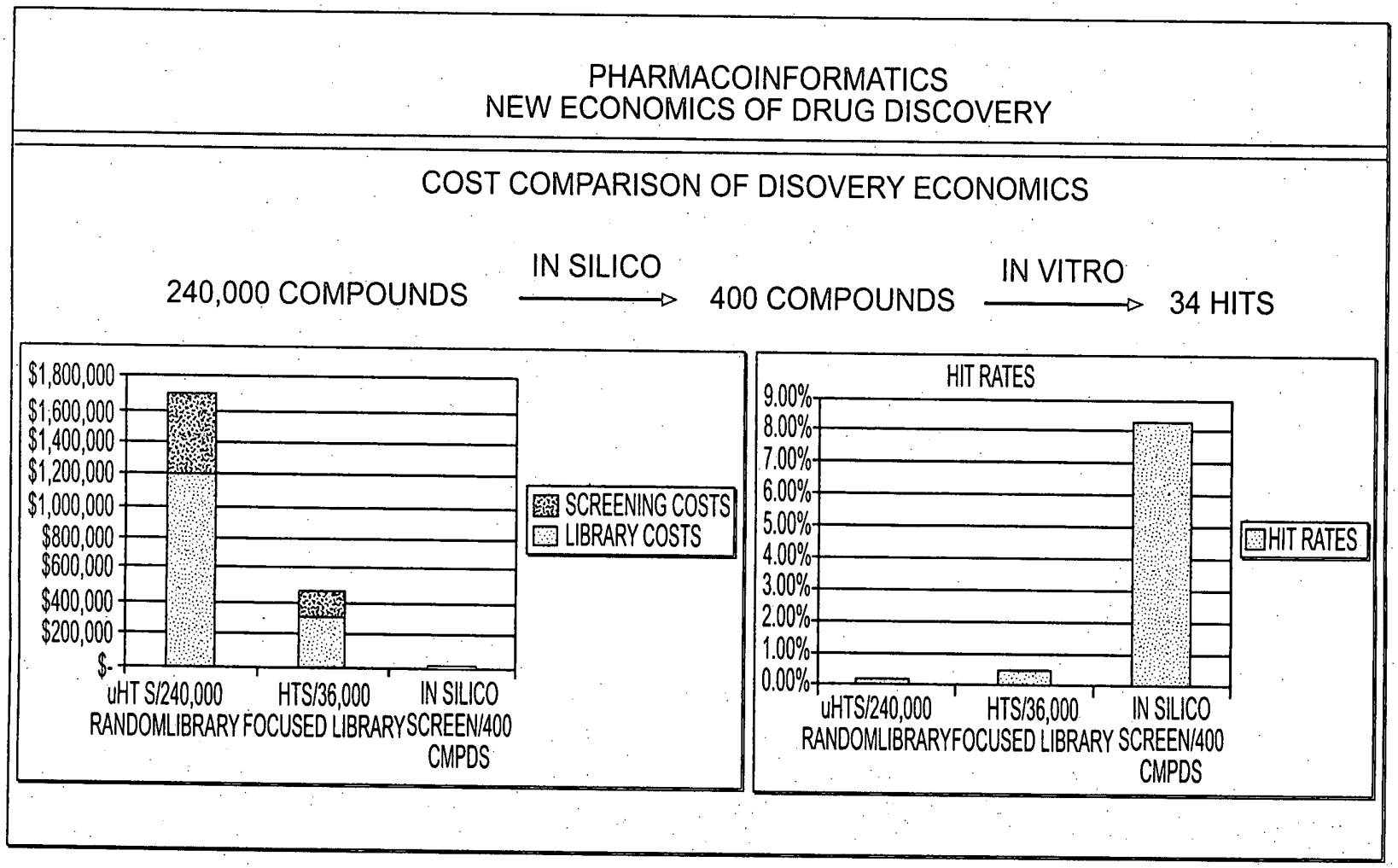

PHARMACOINFORMATICS
NEW ECONOMICS OF DRUG DISCOVERY
COST COMPARISON OF DISOVERY ECONOMICS
240,000 COMPOUNDS
IN SILICO
400 COMPOUNDS
IN VITRO
34 HITS
$1,800,000
$1,600,000
$1,400,000
$1,200,000
$1,000,000
$800,000
$600,000
$400,000
$200,000
$-
SCREENING COSTS
LIBRARY COSTS
uHT S/240,000 RANDOMLIBRARY
HTS/36,000 FOCUSED LIBRARY
IN SILICO SCREEN/400 CMPDS
HIT RATES
9.00%
8.00%
7.00%
6.00%
5.00%
4.00%
3.00%
2.00%
1.00%
0.00%
HIT RATES
uHTS/240,000 RANDOMLIBRARY
HTS/36,000 FOCUSED LIBRARY
IN SILICO SCREEN/400 CMPDS

FIG. 21